UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,967	12/26/2001	Shigeru Kamei	074129-0510	2213

22428 7590 05/30/2008
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
05/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action

The response filed 3/13/08 directs the amendment of claim 1. Claims 1-6, 9, 10 and 17-25 remain pending. Claims 4-6, 9, 10 and 17-25 remain withdrawn from consideration. Claims 1-3 remain under examination.

Applicants' arguments filed 3/13/08 have been considered and found not persuasive.

✧

Claims 1-3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,480,868. Although the conflicting claims are not identical, they are not patentably distinct from each other.

In response, applicants have argued that the rejection be held in abeyance.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have asserted that the compound (recited in the last four lines of claim 1) is an LH-RH antagonist. However, there is no evidence that this is the case. Certainly, other antagonists of LH-RH are known. But the reality in pharmacology is that one cannot "predict" receptor antagonism or even receptor binding merely be viewing the structure of a compound. Minor changes in structure can result in elimination of activity. As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Given the unpredictability of structure/activity relationships, "undue experimenation" would be required of the skilled artisan to use the composition of claim 1 to antagonize LH-RH.

The rejection is maintained.

✧

Claim 1 is objected to. The structural formula is not clearly legible. The examiner can determine applicants' intentions with regard to the structures. However, the persons charged with the task of printing the final document may be unwilling to issue the patent if

the structures are unclear. Accordingly, a notice of allowability will not be issued as long as one or more of the structures is unclear.

✧

Claims 1-3 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 1 recites (line 12) that the copolymer must have a molecular weight of 5-25K. Then, in the second-to-last line, the claim recites that the polymer has a weight of 2000-50000. Given that a weight range of 2000-50000 is not subgeneric to the weight range of 5-25K, clarity is still lacking. Moreover, this lack of clarity will be exacerbated in the event that claim 9 is rejoined. The simplest option would be to delete the last five lines of text from claim 1, and put this information into an independent claim.

✧

The following is a quotation of 35 U.S.C. §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section §102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section §102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each

claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1-3 are rejected under 35 U.S.C. §103 as being unpatentable over Haviv (USP 5,110,904) in view of Deasy (USP 4,874,612) or Hutchinson (USP 4,789,726).

As indicated previously, Haviv discloses (cols 12-25) various peptides falling within the scope of instant claim 1. Also disclosed (col 27, line 8+) is that the peptide can be combined with a PLA/PLG copolymer. Haviv does not suggest selecting a polydispersity that is somewhere in the range of 1.2-4. Each of the secondary references discloses PLA/PGA copolymers that have the requisite polydispersity. For example, this is disclosed in Deasy at col 2, line 45+. Deasy also discloses (col 2, line 45+) the requisite molecular weight. Hutchinson even goes a step further in arguing (col 2, line 51+; col 3, line 53+) that a polydispersity of about 2 is the most statistically probable distribution of molecular weights. A practitioner of the Haviv invention may or may not see an advantage in a polydispersity of 2, but would recognize that such a composition is most likely to be obtained. (Hutchinson also teaches the requisite molecular weight).

In response, applicants have argued that the instant claims are drawn to a method of synthesizing a PLA/PGA copolymer by a method which comprises copolymerizing *alpha* hydroxy acids, and that this method is not disclosed in the references. However, the instant claims are not drawn to a method of preparing a copolymer; rather they are drawn to a combination of a peptide and the copolymer, and there are no limitations on how that copolymer may have been prepared.

Next, applicants have pointed to the following passage in the specification (page 15, line 14+):

> By way of illustration, taking a polymer having a terminal carboxyl group as synthesized from one or more *alpha*-hydroxy acids by the non-catalytic dehydrative poly-condensation process as an example, the number average molecular weight by end-group determination is approximately equal to the number average molecular weight found by GPC. In contrast, in the case of a polymer substantially not containing free terminal carboxyl groups as synthesized from a cyclic dimer by the ring-opening polymerization process and using catalysts, the number average molecular weight by end-group determination is by far greater than the number average molecular weight by GPC determination. By this difference, a polymer having a terminal carboxyl group can be clearly discriminated from a polymer having no terminal carboxyl group. Thus, the term "biodegradable polymer having a terminal carboxyl group" is used herein to mean a biodegradable polymer showing a substantial agreement between the number average molecular weight by GPC determination and the number average molecular weight by end-group determination.

Applicants have also pointed out that the instant claims require that there be at least one carboxyl group present in the PLA/PGA copolymer, and that the references are silent as to the presence or absence of the same.

Consider in particular the following passage (p. 15, specification, line 22+):

> "synthesized from a cyclic dimer by the ring-opening polymerization process and using catalysts".

It is never made clear in the specification what is meant by this. Which dimer, which catalyst, and what reaction conditions? That is, if a chemist wanted to synthesize a PLA/PGA copolymer that has no terminal carboxyl group, how would he go about it, and more importantly, what structure would applicants envisage in which the terminal carboxyl group has been eliminated? At no point in the specification have applicants revealed

the structure of the PLA/PGA copolymer that might lack a terminal carboxyl group. Nor do applicants provide any sort of speculation as to a possibility for a functional group that might be present at the termini (such that a free carboxyl group is not present). Nor do applicants provide any clues as to how a chemist could synthesize a copolymer from lactic acid and glycolic acid, in the absence of all other reactants, such that a carboxyl group is not present. Of course, one could take a LA/GA copolymer that bears a carboxyl group and esterify or amidate the C-terminal carboxyl group by any of a number of procedures. But if applicants are attempting to imply that it is even possible to synthesize a PLA/PGA copolymer that lacks a terminal carboxyl group just be reacting lactic acid and glycolic acid, in the absence of all other reactants and oxidants, such a proposal would be found to be unpersuasive. Further, there is nothing in the instant specification, or even in applicants arguments that would suggest that the PLA/PGA copolymer of Boswell lacks a terminal carboxyl group.

Add to the foregoing another consideration. As stated in the specification (page 15):

> "…the term "biodegradable polymer having a terminal carboxyl group" is used herein to mean a biodegradable polymer showing a substantial agreement between the number average molecular weight by GPC determination and the number average molecular weight by end-group determination…"

Thus, the specification stops short of asserting that ring-opening polymerization of cyclic dimers fails to produce polymers bearing terminal carboxyl groups; what is offered instead is the idle speculation that perhaps some of the polymers might not bear carboxyl groups.

Furthermore, the method by which applicants have determined the presence or absence of carboxyl groups is by a simple titration (page 14, line 33+). This technique may be effective to determine the presence of protonated carboxyl groups; but it is completely ineffective at determining the number of "carboxyl groups", as this term is broadly used.

There is an argument to be made that the textbook definition of a "carboxyl group" is such as to exclude salts of carboxyl groups. But in practice, the term "carboxyl group" and carboxylate anion are used interchangeably by most chemists and biologists. If applicants want to convey that the carboxyl groups must be protonated, it would be a simple matter to introduce this term into the claim.

Further to the foregoing, the claims do not require that all of the polymers bear carboxyl groups (protonated or not). If just 10% of the polymers bear carboxyl groups, that is sufficient to satisfy the requirements of the claims.

If applicants genuinely believe that polymerization of cyclic dimers of lactic/glycolic acid produces polymers that lack carboxyl groups, it is suggested that applicants offer some speculation as to how it is possible for the polymerization to proceed (which it clearly does) but without producing any carboxyl groups or carboxylate anions. This speculation will provide the basis for further discussion.

As matters currently stand, the rejection is maintained.

✦

Claims 1-3 are rejected under 35 U.S.C. §103 as being unpatentable over Haviv (USP 5,110,904) in view of Boswell (USP 3,773,919) further in view of either Deasy (USP 4If ,874,612) or Hutchinson (USP 4,789,726).

The teachings of the references were indicated previously. As noted above, among the references that disclose the requisite molecular weight is Deasy. The rejection is maintained.

✧

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571)272-0562. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

/David Lukton/

Primary Examiner, Art Unit 1654